

# ORAL COMPOSITIONS CONTAINING ANTICALCULUS AND ANTIPLAQUE AGENTS

This application is a continuation-in-part of U.S. application Ser. No. 794,783, filed Nov. 25, 1991, now U.S. Pat. No. 5,208,009, which is a continuation-in-part of U.S. application Ser. No. 631,232, filed Dec. 20, 1990, now U.S. Pat. No. 5,096,699, issued Mar. 17, 1992 and of U.S. application Ser. No. 594,598, filed Oct. 9, 1990 now U.S. Pat. No. 5,158,763.

This invention relates to oral compositions containing anticalculus and antiplaque agents. More particularly, it relates to such compositions which are intended for application to the teeth and which have the desirable properties of effectively inhibiting development of dental calculus, which development can lead to gingivitis, as well as inhibiting plaque formation.

Toothpastes and mouthrinses have been manufactured and sold which have had in their formulas components intended to promote dental health, in addition to components intended primarily to clean the teeth and sweeten the breath. For example, fluorides have been successfully included in dentifrice formulations and in mouthrinses for years to harden teeth and reduce caries development, and triclosan and sanguinaria (bloodroot) extract have been employed in dentifrices to reduce plaque formation on the teeth. Azacycloalkane-2,2-diphosphonic acids (AAP's), especially azacycloheptane-2,2-diphosphonic acid (AHP), and salts thereof (also designated AAP and AHP) have been suggested for incorporation in oral composition to reduce tartar (calculus) and plaque because they have the ability to dissolve or prevent deposition on the teeth of difficultly soluble calcium salts as taught in U.S. Pat. Nos. 3,941,772 and 3,988,443 to Ploger et al. In point of fact AAP's are more effective in reducing calculus than in reducing plaque. Accordingly, oral compositions effective against both calculus and plaque have been difficult to achieve.

In accordance with the present invention an anticalculus and antiplaque oral composition comprises an orally acceptable vehicle or carrier for such composition, an effective amount of an orally acceptable azacycloalkane-2,2-diphosphonic compound (AAP) anticalculus agent and an effective amount of certain antimicrobial agents.

It is a further advantage of this invention that when the antiplaque agent is a cationic antimicrobial (i.e. antibacterial) agent staining or discoloration of dental surfaces is reduced.

Other advantages will be apparent from consideration of the following specification.

Applicants are aware of and call attention to the following patent art of interest:

U.S. Pat. Nos. 3,941,772 and 3,988,443, which relate to azacycloalkane-2,2-diphosphonic acids and their uses in toothpastes and mouthwashes.

Patents starting with British Patent 825,577 to Clemow et al which disclose 1,6-di-4'-chlorophenyl-diguanidohexane (chlorhexidine) as a cationic antimicrobial agent effective to inhibit the effect of oral bacteria which cause plaque formation. Chlorhexidine and numerous other cationic antimicrobial agents have, therefore, been recommended to inhibit plaque formation. However, use of cationic antimicrobial agents has led to the staining or discoloration of dental surfaces.

The reason for the formation of such dental stain has not been clearly established. It is believed, however, that stain results from the entrapment of stain chromophores in dental

calculus. Cationic antimicrobials enhance the staining process by accelerating both the formation of the stain chromophores and the deposition of calculus. This phenomenon is described in A. Gaffar et al., Journal of Dental Research, Vol. 60, No. 8, pp. 1432-1439 (August 1981).

The art has long sought to employ additives which reduce the dental staining properties of antibacterial agents. Thus, for example, in U.S. Pat. No. 3,934,002 to Haeefele the staining properties of bis-biguanide compounds are sought to be inhibited by the inclusion of such compounds as zinc phenol sulfonates hydroxy quinoline, homopolymers and copolymers of aliphatic polycarboxylic acids, certain polyphosphates, certain salts of rare earth metals, phytic acid and certain polyphosphonates and ammonium polyphosphonates. In U.S. Pat. No. 4,042,679 to Gaffar the staining properties of bis-biguanido hexanes and quaternary ammonium salts such as benzethonium chloride and cetyl pyridinium chloride are said to be inhibited by employing as an antistain additive, a polymeric polyphosphonic compound such as polyalkyl bis-(phosphonomethylene) amine acid. In U.S. Pat. No. 4,224,309 to Gaffar et al, the antistaining properties of such bis-biguanido hexanes and quaternary ammonium salts are said to be inhibited by employing as an antistain additive a 2-phosphono-butane-1,2,4-tricarboxylic acid compound. In U.S. Pat. No. 4,118,474 to Gaffar et al, the antistaining properties of such antibacterial agents are said to be inhibited by employing as an antistain additive phosphonoacetic acid and its salts.

For one reason or another, these prior suggestions have not proven to be widely used. For example, previously employed additives which reduced dental staining by cationic antibacterial antiplaque agents also generally reduced their antibacterial and antiplaque activities as by forming a precipitate with such agents.

U.S. Pat. No. 4,022,880 to Vinson et al discloses non-cationic antimicrobial agents such as triclosan (2',4',4'-trichloro-2-hydroxydiphenyl ether, sometimes known as 5-chloro-2-(2,4-dichlorophenoxy) phenol) as antiplaque agents as well cationic antimicrobial agents together with a source of zinc ions, which acts as an anticalculus agent. In German OLS 3532860, triclosan is disclosed in a dentifrice with a copper compound. Other disclosures of triclosan in oral compositions are in EP 0161898, 0161899 and 0220890.

Thus, the present invention of an oral composition with properties to inhibit both calculus and plaque is particularly remarkable. Moreover, when cationic antibacterial agent is employed success against staining is achieved without decreasing the antibacterial, antiplaque activity of the antibacterial agent, a result, which thus far, has eluded the art.

From a review of the art it appears that AAP including AHP and antimicrobial agents including cationic agents such as chlorhexidine and noncationic agents such as triclosan are known dentifrice components separately but no prior art references are known to applicants in which AAP and the antimicrobial agents are present together or in which such preparations are suggested.

The AAP or azacycloalkane-2,2-diphosphonic compound of the invented compositions is an orally acceptable phosphonic acid or salt thereof, which provides a source of an azacycloalkane 2,2-diphosphonate anion. If the salt is employed it will usually be the sodium or potassium salt and will be water soluble. Preparation of AAP is taught in U.S. Pat. No. 3,941,772 to Ploger and its division U.S. Pat. No. 3,988,443, the disclosures of which are incorporated herein by reference. If a salt is to be used it will preferably be one wherein more than one of the phosphonic hydroxyl hydro-